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Fabry disease prevalence in patients with familial Mediterranean fever: A cohort study

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Ethics Committee approval was taken from the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (date: 21/08/20, decision number: 362).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Fabry disease is an X-chromosome inherited disease, which constitutes a rare disease group. Fabry disease has a wide spectrum of symptoms and some of these symptoms that are seen in other diseases. Familial Mediterranean fever (FMF) is a common disease in countries along the Mediterranean coast, including our country. Although typical episodes of recurrent high fever and abdominal pain occur, patients can also present with nonspecific symptoms and signs. This study aimed to investigate the presence of Fabry disease in patients with FMF.

Methods: Information about this cohort study was given to all patients who were followed up with a diagnosis of FMF. Those who agreed to sign the informed consent form were included in the study. Fabry disease screening was performed by galactosidase alpha (GLA) gene analysis in female patients and by examining lysosomal alpha galactosidase A (AGALA) enzyme activity in male patients. When enzyme activity was found to be low in male patients, a GLA gene analysis was also performed.

Results: Fabry disease was screened in a total of 189 patients with familial Mediterranean fever, and it was not detected in any of our patients. Low AGALA enzyme activity was detected in approximately 20% of the male patients. In the GLA gene analysis performed on these patients, any genetic mutation that could be associated with Fabry disease was not detected.

Conclusion: People with Fabry disease or FMF can present with common symptoms, such as arthritis, proteinuria, and abdominal pain. In our study, Fabry disease was not found in any of patients who had a diagnosis of FMF. However, only a few publications on this subject are available. In studies conducted in our country and around the world, it has been shown that GLA gene mutations that may cause Fabry disease can be detected in patients with FMF. However, such a mutation was not detected in our study.

Keywords: Alpha-galactosidase, Fabry disease, Familial Mediterranean fever

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Introduction

Fabry disease is an X-linked lysosomal storage disorder that is characterized by accumulation of globotriaosylceramide and globostriaosylsphingosine within lysosomes in almost all cells [1]. The GLA gene is mutated in Fabry disease that expresses alpha-galactosidase A (AGALA) enzyme activity and is located in the long arm of X chromosome (Xq22.1) [2]. The prevalence of Fabry disease differs among races and is reported to be seen from 1/8500 to 1/117,000 in Caucasian populations [3, 4]. It is known that prevalence of Fabry disease is probably underestimated because of nonspecific manifestations, wrong initial diagnosis, and lack of consideration of this disease by a clinician due to its rare occurrence. The Fabry Outcome Survey showed that rheumatological conditions, arthritis, neuropsychological diseases, Meniere disease, irritable colon, and/or chronic kidney disease of unknown etiology are the most commonly initial diagnoses in a patient with Fabry disease [5, 6]. Patients with Fabry disease may present with a wide spectrum of clinical manifestations. Acroparesthesias, angiokeratomas, abdominal pain, recurrent vomiting, corneal opacities, proteinuria, polyuria, unexplained renal insufficiency, and hypohidrosis are some clinical manifestations of Fabry disease.

Familial Mediterranean fever (FMF) is also a hereditary disorder [7]. A mutation in the pyrin (MEFV) gene causes FMF. FMF is almost always inherited in an autosomal recessive pattern. The MEFV gene is localized within the 16th chromosome and encodes pyrin. Recurrent fever, abdominal pain, chest pain, arthritis, and skin lesions may be seen in a patient with FMF [7–11]. The most important complication of FMF is amyloidosis, which can lead to chronic kidney disease and end stage renal disease [12]. Tel-Hashomer criteria are usually used to diagnose FMF [13]. Since most of the symptoms and signs of FMF are nonspecific, other accompanying diseases may sometimes be overlooked or make some diseases difficult to diagnose [14].

Fabry disease and FMF have some similar manifestations and only a few studies investigating Fabry disease prevalence in patients with FMF are available. In this study, we aimed to investigate Fabry disease prevalence in patients with FMF.

Materials and methods

Patients

All patients who were followed up by our outpatient clinic with the diagnosis of FMF between May 2018 and June 2020 and agreed to participate in this cohort study were included. Diagnosis of all patients was obtained with Tel-Hashomer criteria. Demographic data and clinical features of patients were obtained with face-to-face interviews. MEFV gene mutations were recorded from patients' files. Informed consent was taken from all patients for Fabry disease screening. Local Ethics Committee approval was taken from the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (date: 21/08/20, decision number: 362).

Fabry Disease Screening

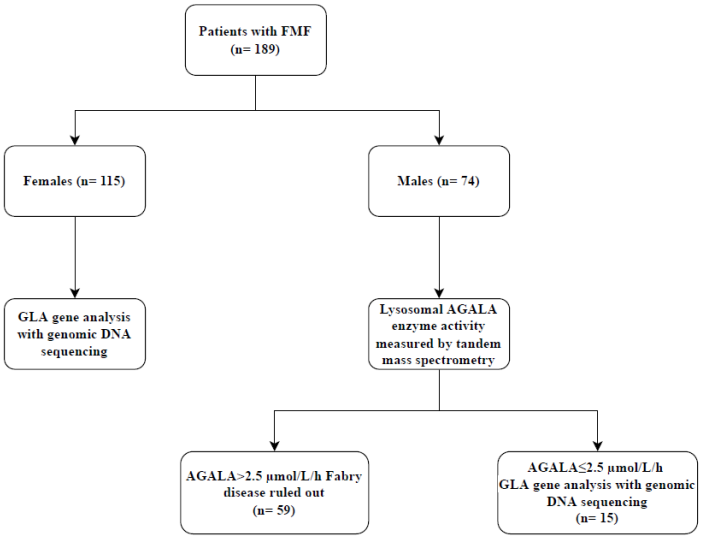
AGALA enzyme activity

Lysosomal AGALA enzyme activity was evaluated in male patients. Samples for enzyme activity were included on dried blood spots (DBS). Tandem mass spectrometry was used as method. AGALA > 1.2 µmol/l/h was considered the cut-off value. GLA gene analysis also was done for male patients having AGALA < 2.5 µmol/l/h.

GLA gene mutation

Peripheral blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes for GLA gene analysis. Analysis was performed using a genomic DNA sequencing method in female patients. Exons 1–7 were examined for all females. Figure 1 shows the method by which patients are screened for Fabry disease.

Figure 1: Fabry disease screening in study patients



Statistical analysis

SPSS 22.0 (SPSS IBM, Armonk, NY, USA) is used for statistical analysis. Categorical variables were expressed as number and percentage. The Shapiro–Wilk test was used to determine normal distribution of continuous variables. Numeric variables were presented as mean (standard deviation) or median (min–max) according to their normality.

Results

The study was conducted with 189 patients with FMF. Of these, 60.8% (n = 115) were female, and 39.8% (n = 74) were male. The median age of patients was 38 years (range: 18–74 years). Patient evaluations in terms of Tel-Hashomer criteria are shown in Table 1.

The results of the MEFV gene analysis are shown in Table 2.

Table 1: FMF characteristics of the patients

Criteria	Present (%-n)
Recurrent febrile episodes associated with serositis	70.4–133
Amyloidosis of AA type	9.5–18
Response to colchicine	94.7–179
Recurrent febrile episodes	74.6–141
Erysipelas-like erythema	18–34
Positive family history	73.5–139

Table 2: Mutations in the pyrin (MEFV) gene

Mutation	%-n
m694v (homozygous)	16.4–31
Wild type	16.4–31
m694v (heterozygous)	15.9–30
m694v (heterozygous), m680i (heterozygous)	10.1–19
m694v (heterozygous), v726a (heterozygous)	7.9–15
e148q (heterozygous)	3.7–7
m680i (heterozygous)	3.7–7
m694v (heterozygous), r761h (heterozygous)	3.2–6
m694v (heterozygous), a744s (heterozygous)	2.6–5
m694v (heterozygous), e148q (heterozygous)	2.6–5
v726a (homozygous)	2.6–5
m680i (homozygous)	2.6–5
m694i (heterozygous), v726a (heterozygous)	2.1–4
m694v (heterozygous), v726a (heterozygous)	2.1–4
v726a (heterozygous)	2.1–4
m680i (heterozygous), v726a (heterozygous)	1.6–3
p369s (heterozygous)	1.1–2
m680i (homozygous) or m694i (heterozygous) or other heterozygous compound	3–6
Total	100–189

Median FMF duration was 6 years (range: 1–40 years). Hypertension was present in 9.5% (n = 18) of the patients, diabetes mellitus in 6.3% (n = 12), chronic kidney disease in 7.9% (n = 15), and coronary artery disease in 0.5% (n = 1). None of the patients had a history of cerebrovascular events.

GLA gene analysis of all female patients was negative. The mean alpha-galactosidase A level of male patients was 4.28 (1.6) μmol/l/h. In 20.3% (n = 15) of male patients, the AGALA enzyme level was ≤ 2.5 μmol/l/h, and GLA gene analysis was also performed for these patients. No mutations were detected in the GLA gene of these male patients.

Discussion

Fabry disease is classified in the rare disease group, and its prevalence differs in studies. The prevalence of Fabry disease is underestimated due to the rarity of the disease, its non-specific symptoms, and the misdiagnosis of patients [4]. In the Fabry Outcome Survey, it was shown that misdiagnosis of Fabry disease is common. Male patients are diagnosed 13.7 years after the first symptom, and female patients are diagnosed 16.3 years after the first symptom [6]. Most patients with FMF experience their first attacks in childhood. The first attack occurs before the ages of 10 and 20 years in 65% and 90% of cases, respectively [7]. Patients with FMF may experience a prodromal period 1–2 days before an attack. Constitutional symptoms, neuropsychiatric or physical signs, appetite and taste alterations, and pain in the region in which the flare-up will appear may be seen in the prodromal period [15]. Our study was designed based on the view that both Fabry disease and FMF have common nonspecific symptoms; however, no patients with Fabry disease in our FMF patients were found.

FMF is a clinical diagnosis, and genetic analysis is not a test used for the diagnosis of FMF. Genetic testing of the MEFV gene show be wild type in some patients with FMF. A wild type MEFV gene does not mean that these patients do not have FMF, but more detailed research may be required to interpret this finding in these patients. The prevalence of Fabry disease varies between studies according to the selected patient group [16–19]. In a study conducted by Zizzo et al. [20], it was shown that 9.4% (n = 3) of FMF patients having a MEFV gene with a single genetic alteration or without any mutation had some exonic mutations in GLA genes responsible for Fabry disease. They concluded that patients with ambiguous symptomatic FMF patterns should be screened for Fabry disease. Lidove et al also showed that two out of 58 patients with Fabry disease had previously been diagnosed with FMF [21]. Huzmeli et al. [22] found a mutation in GLA gene in one out of 177 patients with FMF. The genetic mutation detected in Huzmeli's study was D313Y, which is considered a benign mutation. The D313Y is the most discussed mutation in the literature [23–25]. In fact, some studies have reported false higher prevalence due to D313Y [25, 26]. Fabry disease was not detected in any of the 189 FMF patients in our study. In the TURKFAB study, Turkmen et al. [28] found the incidence of Fabry disease in patients with chronic kidney disease of unknown etiology to be 0.95% (3/313). The study was carried out with focus on chronic kidney patients who did not receive renal replacement therapy, and enzyme replacement therapy was also started in patients with Fabry disease, which could lead to end-stage renal disease. Both FMF and Fabry disease may lead to serious renal complications. Our study was designed based on the premise that Fabry disease and FMF may have similar clinical features. However, Fabry disease was not found in our patients with FMF in this study.

Limitations

The limitations of our study are the single center and the small population of 189 patients with respect to a disease that is common in our country such as FMF is. However, the limited number of publications in the literature investigating the frequency of Fabry disease in patients with FMF makes our study important. More comprehensive studies are needed to investigate the frequency of Fabry in FMF patients.

Conclusion

Fabry disease is an awareness disorder. According to our literature review, our study is the largest study investigating the frequency of Fabry disease in FMF patients. Although mutations that may be associated with Fabry disease were found in the literature in patients with FMF, no FMF patients with Fabry disease were found in our study.

References

1. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;22(5):30. doi: 10.1186/1750-1172-5-30.
2. Bishop DF, Kornreich R, Desnick RJ. Structural organization of the human alpha-galactosidase A gene: further evidence for the absence of a 3' untranslated region. Proc Natl Acad Sci U S A. 1988;85(11):3903-7. doi: 10.1073/pnas.85.11.3903.
3. Branton MH, Schiffmann R, Sabnis SG, Murray GJ, Quirk JM, Altarescu G, et al. Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course. Medicine (Baltimore). 2002;81(2):122-38. doi: 10.1097/00005792-200203000-00003.
4. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281(3):249-54. doi: 10.1001/jama.281.3.249.
5. Houge G, Skarbøvik AJ. Fabrys sykdom--en diagnostisk og terapeutisk utfordring [Fabry disease--a diagnostic and therapeutic challenge]. Tidsskr Nor Laegeforen. 2005;125(8):1004-6.
6. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004;34(3):236-42. doi: 10.1111/j.1365-2362.2004.01309.x.
7. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med. 1967;43(2):227-53. doi: 10.1016/0002-9343(67)90167-2.
8. Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. Arthritis Rheum. 2009;61(10):1447-53. doi: 10.1002/art.24458.
9. Heller H, Gafni J, Michaeli D, Shahin N, Sohar E, Ehrlich G, et al. The arthritis of familial Mediterranean fever (FMF). Arthritis Rheum. 1966 Feb;9(1):1-17. doi: 10.1002/art.1780090102.
10. Drenth JP, van der Meer JW. Hereditary periodic fever. N Engl J Med. 2001;345(24):1748-57. doi: 10.1056/NEJMra010200.
11. Yavuzbilge G, Okuyucu M, Civil Y, Günaydın S, Avcı B. Assessment of serum TWEAK levels in patients with familial Mediterranean fever. J Surg Med. 2021;5(2):140-3. doi: 10.28982/josam.833593
12. Ozdogan H, Ugurlu S. Familial Mediterranean Fever. Switzerland: Springer International Publishing: Chapter 9. The Emerging Treatment in Familial Mediterranean: 2015:137-58.
13. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997;40(10):1879-85. doi: 10.1002/art.1780401023.
14. Tumgor G, El C, Bucak IH, Yilmaz M. Association of Familial Mediterranean Fever and Crohns disease. Dicle Med J. 2013;40:301-3. doi: 10.5798/diclemedj.0921.2013.02.0275
15. Alghamdi M. Familial Mediterranean fever, review of the literature. Clin Rheumatol. 2017;36(8):1707-13. doi: 10.1007/s10067-017-3715-5. Epub 2017 Jun 18.
16. Monserrat L, Gimeno-Blanes JR, Marín F, Hermida-Prieto M, García-Honrubia A, Pérez I, et al. Prevalence of fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2007;50(25):2399-403. doi: 10.1016/j.jacc.2007.06.062.
17. Rolfs A, Fazekas F, Grittner U, Dichgans M, Martus P, Holzhausen M, et al. Acute cerebrovascular disease in the young: the Stroke in Young Fabry Patients study. Stroke. 2013;44(2):340-9. doi: 10.1161/STROKEAHA.112.663708. Epub 2013 Jan 10.

18. Terryn W, Deschoenmakere G, De Keyser J, Meersseman W, Van Biesen W, Wuyts B, et al. Prevalence of Fabry disease in a predominantly hypertensive population with left ventricular hypertrophy. Int J Cardiol. 2013;167(6):2555-60. doi: 10.1016/j.ijcard.2012.06.069.
19. Elliott P, Baker R, Pasquale F, Quarta G, Ebrahim H, Mehta AB, et al. Prevalence of Anderson-Fabry disease in patients with hypertrophic cardiomyopathy: the European Anderson-Fabry Disease survey. Heart. 201;97(23):1957-60. doi: 10.1136/heartjnl-2011-300364.
20. Zizzo C, Colomba P, Albeggiani G, Gallizzi R, Iemolo F, Nuzzo D, et al. Misdiagnosis of familial Mediterranean fever in patients with Anderson-Fabry disease. Clin Genet. 2013;83(6):576-81. doi: 10.1111/j.1399-0004.2012.01940.x.
21. Lidove O, Kaminsky P, Hachulla E, Leguy-Seguin V, Lavigne C, Marie I, et al. Fabry disease 'The New Great Imposter': results of the French Observatoire in Internal Medicine Departments (FIMeD). Clin Genet. 2012;81(6):571-7. doi: 10.1111/j.1399-0004.2011.01718.x.
22. Huzmeli C, Candan F, Alaygut D, Bagci G, Akkaya L, Bagci B, Sozmen EY, Kurtulgan HK, Kayatas M. Prevalence of Fabry Disease in Familial Mediterranean Fever Patients from Central Anatolia of Turkey. Biochem Genet. 2016;54(4):448-456. doi: 10.1007/s10528-016-9731-3.
23. Niemann M, Rolfs A, Giese A, Mascher H, Breunig F, Ertl G, et al. Lyso-Gb3 Indicates that the Alpha-Galactosidase A Mutation D313Y is not Clinically Relevant for Fabry Disease. JIMD Rep. 2013;7:99-102. doi: 10.1007/8904_2012_154. Epub 2012 Jul 1.
24. Effraimidis G, Rasmussen ÅK, Bundgaard H, Sørensen SS, Feldt-Rasmussen U. Is the alpha-galactosidase A variant p.Asp313Tyr (p.D313Y) pathogenic for Fabry disease? A systematic review. J Inherit Metab Dis. 2020;43(5):922-33. doi: 10.1002/jimd.12240.
25. Zompola C, Palaiodimou L, Kokotis P, Papadopoulou M, Theodorou A, Sabanis N, et al. The mutation D313Y may be associated with nervous system manifestations in Fabry disease. J Neurol Sci. 2020;412:116757. doi: 10.1016/j.jns.2020.116757.
26. Froissart R, Guffon N, Vanier MT, Desnick RJ, Maire I. Fabry disease: D313Y is an alpha-galactosidase A sequence variant that causes pseudodeficient activity in plasma. Mol Genet Metab. 2003;80(3):307-14. doi: 10.1016/S1096-7192(03)00136-7.
27. Dubuc V, Moore DF, Gioia LC, Saposnik G, Selchen D, Lanthier S. Prevalence of Fabry disease in young patients with cryptogenic ischemic stroke. J Stroke Cerebrovasc Dis. 2013;22(8):1288-92. doi: 10.1016/j.jstrokecerebrovasdis.2012.10.005.
28. Turkmen K, Guclu A, Sahin G, Kocyigit I, Demirtas L, Erdur FM, et al. Kidney Blood Press Res. 2016;41(6):1016-24. doi: 10.1159/000452605. Epub 2016 Dec 23. PMID: 28006774.

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